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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,931	08/26/2005	Adrian Bot	8114-008-WO-US	7472

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EXAMINER	
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ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
10/01/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,931	BOT ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 77-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 77-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/2/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination(RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission, including a claim amendment and arguments, filed on 9/2/10 has been entered. Claims 2-76 are canceled and new claims 77-92 have been added. Claims 1 and 77-92 are currently pending and under examination in the instant application. It is noted that the claims as amended are now limited to the elected species of pA:pU as the species of dsRNA. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

37 CFR 1.121(c)

The claim listing filed on 9/2/10 is not in compliance with 37 CFR 1.121(c). The claim listing on page 1, after properly identifying claims 2-36 as "cancelled", states "Cancel claims 37-76". This request is not a proper claim listing for claims 37-76 which should have been listed in a similar manner to canceled claims 2-36, e.g. " Claims 37-76 (CANCELLED)". In the interests of compact prosecution the amendment to the claims has been entered. However, future claim listings must comply with the requirements of 37 CFR 1.121(c) or risk non-entry and the receipt of a Notice of Non-Compliant Amendment under 37 CFR 1.121.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 9/2/10 is in compliance with the provisions of 37 CFR 1.97 and 1.98. Accordingly, the information disclosure statement has been considered by the examiner and an initialed and signed copy of the 1449 is attached to this action.

Claim Rejections - 35 USC § 112

The rejection of previously pending claims 1 and 68-76 under 35 U.S.C. 112, first paragraph, for scope of enablement is withdrawn over canceled claims 68-76 and maintained or newly applied to amended and new claims 1 and 77-92. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The claims as amended now recite methods of administering an IgG having at least one MHC-class I restricted T cell epitope of an antigen covalently attached to the IgG backbone without modification of the Fc portion, and the double-stranded RNA pA:pU, wherein a Tc1 response is generated against the antigen.

The previous office action stated that the specification, while being enabling for methods of generating an enhanced Influenza NP specific CD8+ T cell response in a patient comprising administering to the patient by subcutaneous injection a portion of an immunoglobulin comprising a heavy chain containing an Influenza NP CTL epitope replacing the V and CH1 regions and pA:pU, wherein both Tc1 and Tc2 type CD8+ T cells are induced, does not

reasonably provide enablement for generating CD8+ T cells responses using any immunoglobulin comprising any MHC class I peptide epitope, or methods of treating any viral infection or cancer.

The applicant argues that the co-administration of pA:pU with the Ig-class I peptide switches on cross-priming of antigen presenting cells which leads to the differentiation of Tc1 type T cells specific for the class I peptide, and that this phenomenon is not limited to the Influenza NP CTL epitope. In support of this argument, the applicant cites several references as evidence that the limited ability of exogenously applied IgG containing MHC-class I epitopes to stimulate Tc1 response can be overcome by co-administering pA:pU. In support that this switching effect has been confirmed in the published literature, the applicant cites the post-filing article Kurts et al. Unfortunately, Kurts et al. has not been made of record, nor has a copy of the Kurts et al. publication been submitted for the examiner's consideration. As such, applicant's arguments regarding the teachings of Kurts et al. cannot be evaluated and cannot be relied upon as evidence. Likewise, while the applicant has cited the post-filing publication by Wang et al. as evidence that the cross-priming ability of pA:pU is not limited to Ig-NP, this reference has also not been made of record, nor has a copy of the publication been provided for applicant's consideration. As such, applicant's arguments regarding the teachings of Wang et al. cannot be evaluated and cannot be relied upon as evidence. It is suggested that applicant provide copies of the missing references with their next response.

Other evidence referred to by the applicant has been made of record and has been considered by the examiner. The post-filing publication by Bot et al. presents additional work by the applicants using IgNP and pA:pU. This publication, while confirming that an NP CTL

epitope present in the CDR of an Ig molecule can induce interferon-gamma and IL-2 secreting T cells when introduced *in vivo* by subcutaneous injection in combination with pA:pU, and that the T cell generated are effective in preventing the growth of NP expressing tumors *in vivo*, presents no additional evidence concerning epitopes other than the single Influenza NP MHC class I epitope. Regnault et al., cited as evidence that OVA MHC class I peptides can be presented and stimulate induction of CD8+ T cells is cross-priming is induced, actually relates to the effects of contacting dendritic cells with a whole protein antigen-IgG complex. Regnault et al. discloses that the pathway of internalization of an antigen can effect whether it is processed for the MHC class I or MHC class II pathways. They observed that contacting dendritic cells with OVA protein complexed with anti-OVA IgG antibodies *in vitro* resulted in FcgammaR mediated internalization of the complex and the presentation of MHC class I epitopes present in the OVA protein on MHC class I at the cell surface. Regnault et al. did not test whether the OVA-Ig complexes induced Tc1 type T cells *in vivo*. Further, a whole protein/antibody complex is clearly not functionally similar to an Ig molecule modified to contain within it a single heterologous MHC class I epitope. The rejection of record cited Bona et al. (1999 patent), Zaghouni et al., and Zanetti et al. as all providing evidence that the administration of Ig comprising a heterologous MHC class I epitope did not present peptide-MHC class I complexes and failed to stimulate any peptide specific CD8+ T cells. Thus, the teachings of Regnault et al. concerning protein immune complexes does not overcome the evidence of record. Bonifaz et al. likewise concerns the effects of a protein immune complex, in this case OVA protein chemically coupled to an anti-DEC-205 antibody to target the DEC-205 protein on dendritic cells. Bonifaz et al. actually tested the complex *in vivo* and showed although MHC class I peptides present in

the OVA protein were processed for MHC class I presentation, the OVA:anti-DEC-205 antibody complex tolerized T cells unless it was administered with an anti-CD40 antibody. However, this data is not found to be persuasive to demonstrate that MHC peptide epitopes other than NP can be effective in the instant methods since a conjugated whole protein immune complex which is internalized using a receptor other than an Fc receptor is not functionally equivalent to Ig comprising a heterologous MHC class I epitope because, as noted above, the latter does not lead to MHC class I loading in the absence of pA:pU. Further, there is no evidence of record that receptors that bind dsRNA like pA:pU and CD40 have similar effector functions. Therefore, based on the above analysis, the references provided as evidence by the applicant are not found persuasive in demonstrating enablement for more than the identified scope.

The applicant further argues that that working examples and the post-filing Bot et al. publication provide ample enablement for treating viruses and tumors using the instant methods as claimed and that immunogenic MHC class I peptides derived from tumor antigens were known in the art, citing Scanlan et al. In response, the working examples have been fully considered as discussed in the rejection of record and provide enablement for the identified scope. Bot et al. (2006), discussed above, adds nothing since it uses the same Ig-NP used in the working examples in the instant specification. Further, the issue for lack of enablement beyond the scope identified for treating any virus or tumor as claimed was not based on a lack of enablement for identifying an immunogenic MHC class I peptide derived from a tumor antigen. The rejection of record states that at the time of filing, the literature teaches that the strength and character of an immune response to a particular antigen significantly effects the efficacy of that immune response to treat disease symptoms. As a result, even a strong CTL response may be

insufficient to treat an infection in the absence of a humoral response. For example, Yasutomi et al. teaches that immunization of rhesus monkeys with a live viral vector which encodes the SIV gag protein generates a non-protective CTL response, and further fails to generate a humoral immune response despite the presence of MHC class II and antibody binding epitopes in the gag protein (Yasutomi et al. (1995) J. Virol., Vol. 69 (4), page 2279, abstract). In addition, Yasutomi et al. teaches that while boosting vaccinated animals with a gag peptide/liposome complex significantly increases the anti-gag CTL response, it still did not provide increased protection against SIV challenge (Yasutomi et al., supra, abstract). The situation is even more complicated in the case of raising therapeutic immune responses against tumors. In order for a cytolytic T cell to kill a target tumor cell, the tumor cell must be presenting sufficient amounts of specific peptide/MHC class I complexes on the cell surface. The literature teaches that tumors evade immune response by a variety of mechanisms including loss of antigenic epitopes by either lack of expression or mutations, loss of functional b2m expression or of particular MHC class I alleles, and down-regulation of putative antigen processing molecules, including TAP and MHC-encoded proteosome components (Restifo et al (1993) J. Immunother., Vol. 14, page 183, col 1, lines 8-14, and page 184, col. 2). Erdile et al. further provides a demonstration of difficulties in generating therapeutic CTL against an endogenous cancer antigen. Erdile et al. teaches that administration of a p53 class I peptide and anti-CD40 antibody, while stimulating a detectable CTL response that recognized target cells pulsed with the same p53 peptide, did not generate CTL that could recognize tumor cells presenting endogenous p53 antigen (Erdile et al. (2000) Cancer Immunology Immunotherapy 49 (8): 410-416). The applicant has not addressed any of the issues set forth above as evidenced by Restifo et al., Erdile et a, and Yasutomi et al.,

and Scanlan et al. is silent as to these issues. Therefore, applicant's arguments are not found persuasive in demonstrating enablement of the claimed invention for treating viruses or tumors beyond the identified scope.

Finally, in response to applicant's discussion of the requirements for enablement under 35 U.S.C. 112, first paragraph, and the factors to be considered in determining enablement, it is noted that the previous office actions analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of the skilled artisan, and 8) the breadth of the claims, and presented detailed scientific reasons supported by citation of publications from the prior art for the finding of a lack of enablement for the scope of the invention as claimed. It is also noted that case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). 35 U.S.C. 112 also requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

Therefore, for the reasons set forth above and in previous office actions, the rejection of record stands.

The rejection of claims 1, and 72-75 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of the cancellation of claims 72-75 and the amendments to claim 1.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, the technology center fax number is (571) 273-8300. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633